

The expression of genes coding for positive acute-phase proteins in the reproductive tract of the female rat

High levels of ceruloplasmin mRNA in the uterus

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High levels of ceruloplasmin mRNA were measured in the uterus of both pregnant and non-pregnant rats. No mRNA for α_2 -macroglobulin and α_1 -acid glycoprotein could be detected in the uterus in contrast to the high levels of those two mRNAs found in the decidua in the mid-gestation period. Synthesis of plasma proteins with a protective function in the decidua or uterus may be important in maintaining homeostasis at different stages of reproduction. In addition, ceruloplasmin synthesis by the uterus may be part of a system transporting copper to the fetus.

Development; Acid glycoprotein, α_1 -; Ceruloplasmin; Macroglobulin, α_2 -; Transferrin; Copper metabolism; (Decidua, Uterus)

1. INTRODUCTION

Positive acute-phase proteins, increasing in blood during acute inflammation, have a protective function and help to maintain homeostasis in the extracellular space [1]. The placenta contains high levels of α_2 -macroglobulin, a positive acute-phase protein in the rat. This mRNA is localized in the decidua [2]. The decidua is formed when cells in the uterine endometrium proliferate to surround the embryo after implantation, and is thought to have a protective and nutritive function [3]. Since homeostasis is challenged similarly during both interactions between embryo/uterus and during inflammation, we investigated expression of other positive acute-phase proteins in uterus and decidua.

2. EXPERIMENTAL

Dissection of decidual tissue from fetus and uterus [2,4,5],

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RNA purification, Northern gel analysis and cDNA clones have been described [6–9].

3. RESULTS

3.1. *Expression of transferrin and ceruloplasmin in the liver, uterus, placenta and yolk sac*

Total RNA was purified from liver (10 male rats), uterus (10 rats), placenta and visceral yolk sac (1 litter at 19 days of gestation). Northern gel analysis was used to analyze specific mRNAs. High levels of ceruloplasmin mRNA (approx. 50% of those in liver) were detected in the uterus (fig. 1), low levels in yolk sac and very low levels in placenta (fig. 1). The similarity of the ratio of signal intensity from the high molecular mass band (fig. 1) to the signal from the major band in liver and uterus could suggest that these correspond to precursors for the mature mRNA. Total RNA was purified from sections of uterus opposite to the placenta, dissected from rats at 19 days of gestation, and shown by Northern analysis to contain ceruloplasmin mRNA (fig. 2). Only very low levels

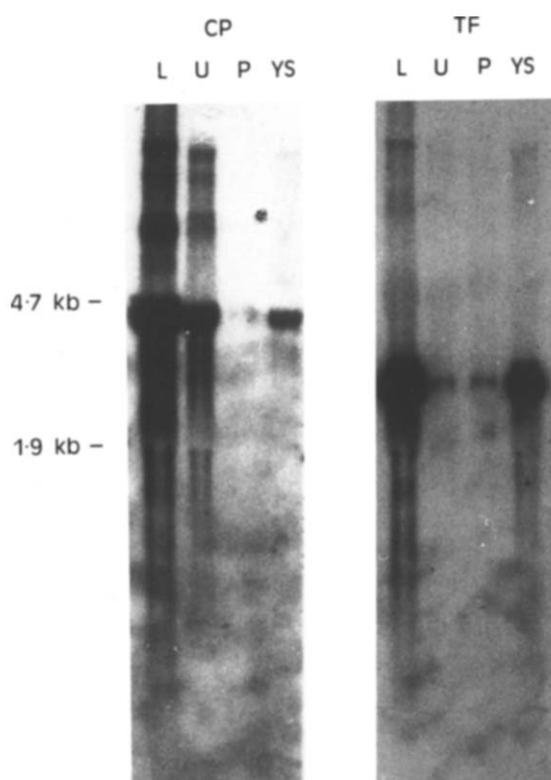


Fig.1. Northern analysis of the expression of the genes for ceruloplasmin (CP) and transferrin (TF). Hybridization of total RNA (15 μ g) from uterus (U), placenta (P), liver (L), and visceral yolk sac (YS). Autoradiography at -70°C with intensifying screen, exposure for 2 weeks (ceruloplasmin) and 1 day (transferrin).

of transferrin mRNA were detected in uterus and placenta (fig.1), in contrast to much higher levels in yolk sac. Some mRNA in placenta samples may originate from contaminating yolk sac.

3.2. α_2 -Macroglobulin and α_1 -acid glycoprotein gene expression in uterus and decidua

In contrast to high levels in decidua [2,10], no mRNA for α_2 -macroglobulin or α_1 -acid glycoprotein was detected in uterus of non-pregnant rats. Maximum levels (table 1) of both α_2 -macroglobulin and α_1 -acid glycoprotein mRNA are found at about 11.5 days after conception (fig.3). However, the time period for which these high levels of α_1 -acid glycoprotein are observed in the decidua during gestation was much shorter than that for α_2 -macroglobulin.

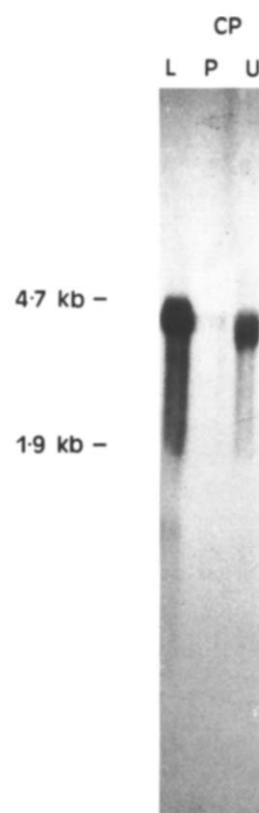


Fig.2. Northern analysis of the ceruloplasmin mRNA levels in uterus during pregnancy. Hybridization of total RNA (15 μ g) from maternal liver (L), placenta (P) and uterus (U).

Table 1

Summary of plasma protein gene expression in female reproductive tract

mRNA	Tissue	Level (maximum detected)
Ceruloplasmin	uterus	50% of liver
Transferrin	uterus	~1% of liver
α_2 -Macroglobulin	decidua	165% of acute-phase liver max.
	uterus	not detected
α_1 -Acid glycoprotein	decidua	30% of acute-phase liver max.
	uterus	not detected

Maximum levels of plasma protein mRNA in decidua and in uterus are shown as a percentage of the value in normal or acute-phase liver

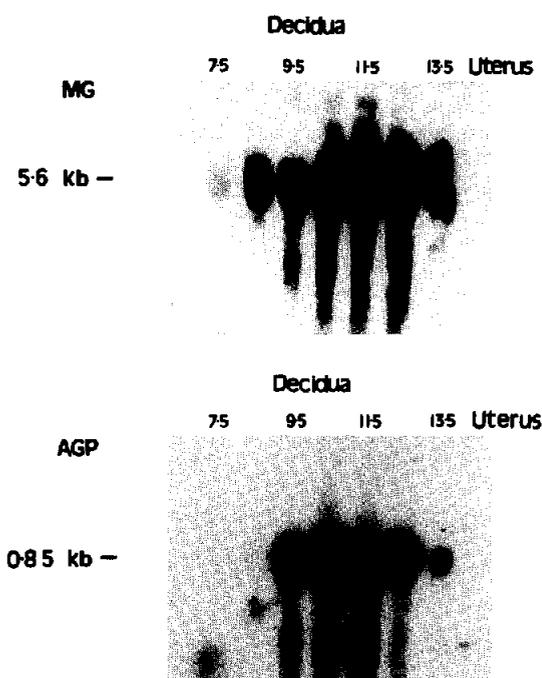


Fig.3. Northern analysis of the expression of α_2 -macroglobulin (MG) and α_1 -acid glycoprotein (AGP) in decidua from 7.5–13.5 day post-conception, and uterus. 15 μ g total RNA; autoradiography for 1 day at -70°C with intensifying screen.

4. DISCUSSION

Development involves extensive tissue remodeling, and this occurs, for example, when the decidua capsularis begins to degenerate [5]. High levels of α_2 -macroglobulin are found in the decidua at this stage. The expression of proteinase inhibitors by intact decidua cells may help to control proteolytic processes involved in removing cell debris. Integration of the destruction of some parts of tissue with the growth of other surrounding parts of tissue is a common feature of both nidation and inflammation. It is likely that the local function of α_1 -acid glycoprotein and α_2 -macroglobulin synthesized by the decidua during nidation is similar to their function during inflammation.

High levels of ceruloplasmin mRNA were observed in the uterus of both pregnant and non-pregnant rats. Transferrin mRNA was also detected in rat uterus. Transferrin mRNA is found in low levels in muscle tissue [8,11], however

ceruloplasmin mRNA was not detected in tissues such as stomach or intestine [9] containing smooth muscle similar to the uterus. This suggested that ceruloplasmin has a specific function in the uterus. Ceruloplasmin is a copper-containing positive acute-phase glycoprotein with ferroxidase activity and may be involved in the mobilization of Fe^{2+} from the liver. It can also catalyse oxidation of catecholamines and may protect tissues from oxidative damage during wound healing [12]. The various enzymatic activities of ceruloplasmin may be useful in the uterus, where the epithelial layer is degraded and replaced during the estrus cycle.

Ceruloplasmin may act as a source of copper for most tissues [13]. After about 15 days of gestation the decidua capsularis and Reichert's membrane break down, leaving the yolk sac epithelium in direct contact with the uterine epithelium [14]. The yolk sac is active in uptake and degradation of exogenous proteins [15]. Ceruloplasmin synthesized in the uterus could be taken up by the visceral yolk sac endoderm cells and supply copper to the growing fetus. Thus, during development, copper is probably transported to the fetus via ceruloplasmin.

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